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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/506,725	09/04/2004	Daniel W Chan	57203(71699)	7047

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EXAMINER	
JOYCE, CATHERINE	

ART UNIT	PAPER NUMBER
1642	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,725	CHAN ET AL.	
	Examiner	Art Unit	
	Catherine M. Joyce	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 June 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-57* is/are pending in the application.

4a) Of the above claim(s) *14,15,20,22 and 37-57* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-13, 16-19, 21, and 23-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/15/2006*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

1. Claims 1-57 are pending, claims 14-15, 20, 22, and 37-57 are withdrawn from consideration as drawn to a non-elected invention, and claims 1-13, 16-19, 21, and 23-36 are being examined.

2. Applicant's election without traverse of the invention of Group II, and of the species of managing treatment by "ordering more tests", a breast cancer status of "the subject's risk of cancer", a known breast cancer biomarker of "CA 15.3", a substrate of a "a microtiter plate comprising biospecific affinity reagents", measuring that is "quantifying the amount of marker", a biochip array that is "a protein biochip array", and "the protein biomarkers are measured by immunoassay" in the reply filed on June 5, 2007 is acknowledged.

3. It is noted that the recitation in claim 3 of the term "ordering more rests" within the phrase "wherein managing subject treatment is selected from ordering more rests, performing surgery, and taking no further action" appears to be a typographical error in that page 4, lines 26-27, of the specification and the response filed on June 5, 2007 indicate that the term should likely be "ordering more tests". Thus, for examination purposes, the term is assumed to be "ordering more tests" rather than "ordering more rests". Applicant is invited to inform the Examiner if this assumption is incorrect.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. In particular, page 1, lines 24-25, and page 61, line 13, are noted. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-13, 16-19, 21, 23-31, and 34 are rejected under 35 U.S.C. 112, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to the following:

A method of qualifying breast cancer in a subject comprising:
(a) measuring at least one biomarker **in a sample** from a subject, and
(b) correlating the measurement with breast cancer status,
wherein the biomarker is Marker III (BC3) (**claim 1**),

further comprising:
(c) managing subject treatment based on the status (**claim 2**),

further comprising:
(c) managing subject treatment based on the status,
wherein managing subject treatment is ordering more tests (**claim 3**),

further comprising:
(c) managing subject treatment based on the status,
further comprising:
(d) measuring the at least one biomarker after subject management (**claim 4**).

wherein the breast cancer status is the subject's risk of cancer (**claim 5**),

wherein measuring comprises detecting by mass spectrometry (**claim 6**),

wherein at least one biomarker is Marker III (BC3) (**claim 7**),

further comprising measuring a known breast cancer biomarker in a sample from the subject and correlating measurement of the known biomarker and the measurement of Marker III (BC3) with breast cancer status (**claim 8**),

further comprising measuring a known breast cancer biomarker in a sample from the subject and correlating measurement of the known biomarker and the measurement of Marker III (BC3) with breast cancer status,

wherein the known biomarker is CA15.3 (**claim 9**),

comprising measuring Marker I (BC 1), Marker II (BC2), and Marker III (BC3) (**claim 10**),

comprising measuring Marker I (BC 1), Marker II (BC2), and Marker III (BC3),

further comprising measuring a known breast cancer biomarker in a sample from the subject and correlating measurement of the known biomarker and the measurement of any one or more of Markers I through XIV with breast cancer status (**claim 11**),

comprising measuring Marker I (BC 1), Marker II (BC2), and Marker III (BC3),

further comprising measuring a known breast cancer biomarker in a sample from the subject and correlating measurement of the known biomarker and the measurement of any one or more of Markers I through XIV with breast cancer status,

wherein the known biomarker is selected from CA 15.3 (**claim 12**),

wherein measuring comprises:

(a) providing a subject sample of blood or a blood derivative;

(b) capturing Marker III from the sample on a surface of a substrate comprising capture reagents that bind the protein biomarkers (**claim 13**),

wherein measuring comprises:

(a) providing a subject sample of blood or a blood derivative;

(b) capturing Marker III from the sample on a surface of a substrate comprising capture reagents that bind the protein biomarkers,

wherein the substrate is a microtiter plate comprising biospecific affinity reagents that bind Marker III and the protein biomarkers are detected by immunoassay (**claim 16**),

wherein measuring is quantifying the amount of marker(s), (**claim 17**),

wherein at least one biomarker is measured using a biochip array (**claim 18**),

wherein at least one biomarker is measured using a biochip array, wherein the biochip array is a protein chip array (**claim 19**),

wherein at least one biomarker is measured using a biochip array, wherein at least one biomarker is immobilized on the biochip array (**claim 21**),

wherein the protein biomarkers are measured by immunoassay (**claim 23**),

wherein the correlating is performed by a software classification algorithm (**claim 24**),

wherein the sample is selected from blood, serum and plasma (**claim 25**),

A method comprising:

(a) measuring a plurality of biomarkers in a sample from the subject, wherein the plurality of biomarkers is selected from the group consisting of: Marker I (BC1), Marker II (BC2), Marker III (BC3), Marker IV, Marker V, Marker VI, Marker VII, Marker VIII, Marker IX, Marker X, Marker XI, Marker XII, Marker III, and Marker XIV *(**claim 26**)*,

wherein the plurality includes Marker I (BC1), Marker II (BC2), and Marker III (BC3) (**claim 27**),

further comprising measuring a known biomarker (**claim 28**),

wherein the known biomarker is CA 15.3 (**claim 29**),

wherein the protein biomarkers are detected by immunoassay (**claim 30**),

wherein the sample is selected from blood, serum and plasma (**claim 31**)

A method comprising:

(a) measuring at least one biomarker in a sample from a subject, wherein the biomarker is Marker III (BC3),

further comprising measuring a known biomarker, wherein the known biomarker is CA 15.3 (**claim 34**),

It is noted that the specification teaches that "breast cancer status" refers to the status of the disease in the patient and that examples of types of breast cancer status include, but are not limited to, the subject's risk of cancer, the presence or absence of disease, the state of disease in a patient, and the effectiveness of treatment of disease (page 5, lines 5-9). Thus, for examination purposes the terms "qualifiying breast cancer" and "breast cancer status" are interpreted to include assessing the disease state in the subject, including lymph node involvement, metastasis and tumor burden, and assessing the subject's risk of breast cancer.

The specification teaches that mass spectrometry protein profiles of serum specimens from stages 0-I breast cancer were compared against those of non-cancer controls to identify potential cancer biomarkers that can detect early breast cancer (Examples 1-3). The specification further teaches that the ability of these identified biomarkers to detect breast cancer was independently tested using samples from Stage II and III cancer patients and that the top scoring peaks were BC1, BC2 and BC3 (Examples 1-3). The specification further teaches that BC1 (also designated as Marker I) has a molecular weight of 4.3 kD, that BC2 (also designated as Marker II) has a molecular weight of 8.1 kD and that BC3 (also designated as Marker III) has a

molecular weight of 8.9 kD (page 3). The specification further teaches that the BC3 marker identified 88% of stage 0-I patients, 78% of stage II patients, and 92% of stage III patients and that a composite analysis using the BC1, BC2 and BC3 markers identified 93% of stage 0-I patients, 85% of stage II patients, and 93% of stage III patients. The specification further teaches that the composite analysis using the BC1, BC2 and BC3 markers showed a high sensitivity (93%) and specificity (91%) and that the detection of the 8.9 kD protein performed the best of the individual markers with a sensitivity of 85% and a specificity of 91% (Example 6). The specification further teaches that in an analysis of ductal carcinoma in situ sample and lobular carcinoma in situ samples, the expression patterns of two of the markers (the 8.9 kD protein and the 8.1 kD protein) were consistent with previous results (Example 6). The specification contemplates, in one aspect of the invention, that the patient sample is selected from the group consisting of blood, blood plasma, serum, urine, tissue, cells, organs and vaginal fluids (page 8, lines 4-6). The specification further teaches that the sample is preferably a biological fluid sample, and that examples of a biological fluid sample blood, blood serum, plasma, nipple aspirate, urine, tears, saliva, etc. (page 32, lines 23-25).

The teaching of the specification cannot be extrapolated to enable the scope of the claims because one of skill in the art could not predict that the broadly claimed method of qualifying breast cancer would function as claimed. In particular, the art teaches that an independent validation of the previously identified breast cancer biomarkers (BC1, BC2, and BC3) shows that BC3 was identified as being anaphylatoxin C3a lacking the C-terminal region (i.e. $C3a_{desarg}$) and BC2 was identified as being a C-terminal-truncated form of $C3a_{desarg}$, wherein C3 is a molecule of the human complement system that is cleaved into C3b and C3a, wherein C3a is very short lived in serum and is cleaved immediately into the more stable $C3a_{desarg}$ (Li et al., 2005, Clinical Chemistry 51(12):2229-2235; page 2229 and 2233). Li et al. also teaches that higher C3 concentrations were reported with neuroblastoma patients and that higher complement concentrations were reported in patients with lung digestive tract, and brain

tumors (page 2234). Li et al. also teaches that the BC1 marker was not confirmed because previous studies (i.e. the instant specification and Li et al., 2002, Clinical Chemistry 48:1296-1304) showed a BC1 decrease in breast cancer whereas the Li et al., 2005, teaches that an increase of BC1 was associated with cancer (page 2231). Further, in commenting on the studies of Li et al. (2005), Diamandis (2006, Clinical Chemistry 52(4):771) notes that there was no difference between patients with benign breast disease and invasive cancer for BC2 and that there was no difference among patients with benign breast disease, ductal carcinoma in situ, of invasive carcinomas for BC3 (page 771). Diamandis further teaches that C3 is a high abundance serum protein whose serum concentration is increased or decreased in a wide variety of clinical conditions and that proteolytic processing of peptides in circulation by peptidases are well known and it should not be surprising that the identified molecules represent modified or truncated forms of C3a (page 771). Diamandis concludes that the BC2 and BC3 markers are likely non-specific biomarkers of acute phase reactions and are likely of questionable clinical value (page 771).

Thus given the teaching in the art that the marker BC1 was not validated, that BC2 and BC3 were not able to distinguish between benign breast disease and cancer, that complement, C3, and C3a are levels are known to vary in variety of clinical conditions and acute phase reactions, and that proteolytic cleavage of circulatory proteins is known to be prevalent, one of skill in the art could not predict that measuring BC3 levels or BC2 levels, i.e. proteolytic products of C3 and C3a, would be useful in qualifying breast cancer as claimed because altered levels of BC3 or BC2 are likely to be found in benign breast disease or in other clinical conditions as taught by Diamandis. Thus, practice of the invention would require undue experimentation.

9. If the rejection of claims 1-13, 16-19, 21, 23-31, and 34, under 35 USC 112, first paragraph, set forth in paragraph 8 above is overcome, the claims would still be rejected under 35 USC 112, first paragraph, because the specification, while being enabling for a method of qualifying breast cancer in a subject comprising: (a) measuring

at least one biomarker in a sample from a subject, and (b) correlating the measurement with breast cancer status, wherein the biomarker is Marker III (BC3) protein, or Marker III (BC3) protein in combination with Marker II (BC2) protein, wherein qualifying is assessing the presence or absence of disease, wherein the sample is a blood, serum or plasma sample, does not reasonably provide enablement for a method of qualifying breast cancer in a subject comprising: (a) measuring at least one biomarker in a sample from a subject, and (b) correlating the measurement with breast cancer status, wherein the biomarker is Marker III (BC3) in combination with any biomarkers I or IV-XIV, wherein the disease status is other than assessing the presence or absence of disease, or wherein the sample is any sample other than blood, plasma, or serum.

In a first aspect, Li et al. (2002, Clinical Chemistry 48:1296-1304) teaches that for the three biomarkers identified in the instant specification BC1, BC2 and BC3, no significant correlation was found between concentrations of the makers and tumor size or lymph node metastasis and that the discriminatory power of these markers most likely reflects the malignant nature of the tumor rather than its progression. Further, one of skill in the art could not predict that the invention would function as claimed in correlating marker levels with breast cancer status wherein breast cancer status is the subject's risk of cancer (i.e. claim 5). In particular, Tockman et al (Cancer Res., 1992, 52:2711s-2718s) teach considerations necessary in bringing a cancer biomarker to successful clinical application wherein prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials (see abstract). Pertinent to the instant rejection, there is no evidence presented in the specification or the art of record that the claimed markers are associated with a subject's risk of cancer. Tockman goes on to teach that markers have clear biological plausibility and if validated (emphasis added) can be used for population screening (p. 2713s, col 1). The essential element of the validation of a marker is the ability to test the marker on clinical material obtained from subjects monitored and to link those marker results with subsequent clinical

confirmation of breast cancer. Given that that the art teaches a lack of correlation between the BC3 marker and cancer progression, one of skill in the art could not predict that measuring BC3 levels would be used to qualify any aspect of breast cancer other than the presence or absence of cancer. Further, given the art recognized need to validate cancer markers, and the lack of guidance in the specification on this issue with regard to determining risk of cancer, one of skill in the art could not predict that the invention would function as broadly claimed in qualifying risk of cancer. Thus, practice of the invention would require undue experimentation.

In a second aspect, one of skill in the art could not predict that detection of the BC3 protein would function in qualifying breast cancer in combination with any of Markers I or IV-XIV. In particular, as set forth above, Li et al. (2005, Clinical Chemistry 51(12):2229-2235) teaches that the BC1 marker (Marker I) was not confirmed because previous studies (i.e. the instant specification and Li et al., 2002, Clinical Chemistry 48:1296-1304) showed a BC1 decrease in breast cancer whereas the Li et al., 2005, teaches that an increase of BC1 was associated with cancer. Further, Stites et al (Basic and Clinical Immunology, 9th Ed, Appleton and Lange, Norwalk, 1991, page 250-251) specifically teaches that when any diagnostic test is used to make a decision, there is some probability of drawing an erroneous conclusion and that diagnostic sensitivity is defined as the fraction of diseased subjects with abnormal test results and that diagnostic specificity is defined as the fraction of nondiseased subjects who have a normal laboratory test. Thus, without further information on the sensitivity or specificity of the markers IV-XIV, one of skill in the art could not predict that these markers would useful in qualifying breast cancer in conjunction with the BC3 marker, and practice of the invention would require undue experimentation.

In a third aspect, one of skill in the art could not predict that measuring the BC3 in any sample other than blood, serum or plasma would be useful in qualifying breast cancer. The specification teaches, as set forth above, an association between BC1 and BC3 protein levels in a mass spectrometry analysis of serum from breast cancer

patients as compared to the protein levels in health controls. However, this teaching in the specification is not sufficient to establish that an analysis of any sample type from a subject would qualify breast cancer. In particular, Derycke (2006, International Journal of Cancer 119(12):2895-2900) teaches that an analysis of N-cadherin showed a higher concentration of soluble N-cadherin in serum of prostate cancer patients than in healthy persons and that soluble N-cadherin was also present in urine and seminal fluid but was not found in synovial fluid and spinal fluid. Thus, one of skill the art could not predict that a cancer biomarker that was at detectably higher levels in serum could also be found at detectably higher levels in other sample from a subject, including any other body fluid sample. Further, the term "blood derivative", when given its broadest reasonable interpretation includes products such as hemoglobin, fibrin, and blood albumin in addition to serum and plasma. There is no objective evidence or reason to expect that the disclosed biomarkers would persist in such "blood derivatives" which have been subjected to physical and biochemical separations in order to prepare the fractionated blood products. Thus practice of the invention would require undue experimentation.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 32-33 and 35-36 are rejected under 35 U.S.C. 102(b) as being anticipated by Murray et al. (1997, Journal of Lipid Research 38:2492-2501), as evidenced by Li et al. (2005, Clinical Chemistry 51(12):229-2235).

The claims, as drawn to the elected invention, are as follows:

A method comprising:

(a) measuring at least one biomarker in a sample from a subject, wherein the biomarker is Marker III (BC3) *(**claim 32**)*,

further comprising measuring a known biomarker (**claim 33**),

wherein the protein biomarkers are detected by immunoassay (**claim 35**),

wherein the sample is selected from blood, serum and plasma (**claim 36**).

Murray et al. teaches that $C3a_{desArg}$ (molecular weight 8932.5) is biologic fragment of complement C3 produced through the alternate complement pathway and is also known as acylation stimulation protein (ASP) (page 2492). As evidenced by Li et al., BC3 of the instant invention is $C3a_{desArg}$ (page 2229). Murray et al. teaches that fractions obtained during purification of recombinant ASP were separated on 15% SDS-PAGE and stained with Coomassie blue, including control plasma ASP (page 2495, Figure 1), using known molecular biomakers. Murray et al. also teaches a western blot analysis of purified ASP using an anti-ASP antibody. Thus, all of the claim limitations are met.

12. No claims are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Catherine M. Joyce whose telephone number is 571-272-3321. The examiner can normally be reached on Monday thru Friday, 10:15 - 6:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shanon Foley, can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Karen A. Canella/
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